

## Supplementary Online Content

Oxnard GR, Wilcox KH, Gonen M, Polotsky M, Hirsch BR, Schwartz LH. Response rate as a regulatory end point in single-arm studies of advanced solid tumors. *JAMA Oncol*. Published online February 25, 2016. doi:10.1001/jamaoncol.2015.6315

**eTable 1.** Characteristics of trial arms studied

**eTable 2.** Single agents with the highest max objective response rate (ORR) statistically exceeded

**eFigure 1.** 1800 trials studying colorectal, renal, lung, and skin malignancies were identified from a database of 8942 oncology trials

**eFigure 2.** Receiver operating characteristic (ROC) curves describing the characteristics of maximum (red) and mean (black) objective response rate (RR) as diagnostic tests for the prediction of regulatory approval

**eMethods.** R code of the statistical analyses

This supplementary material has been provided by the authors to give readers additional information about their work.

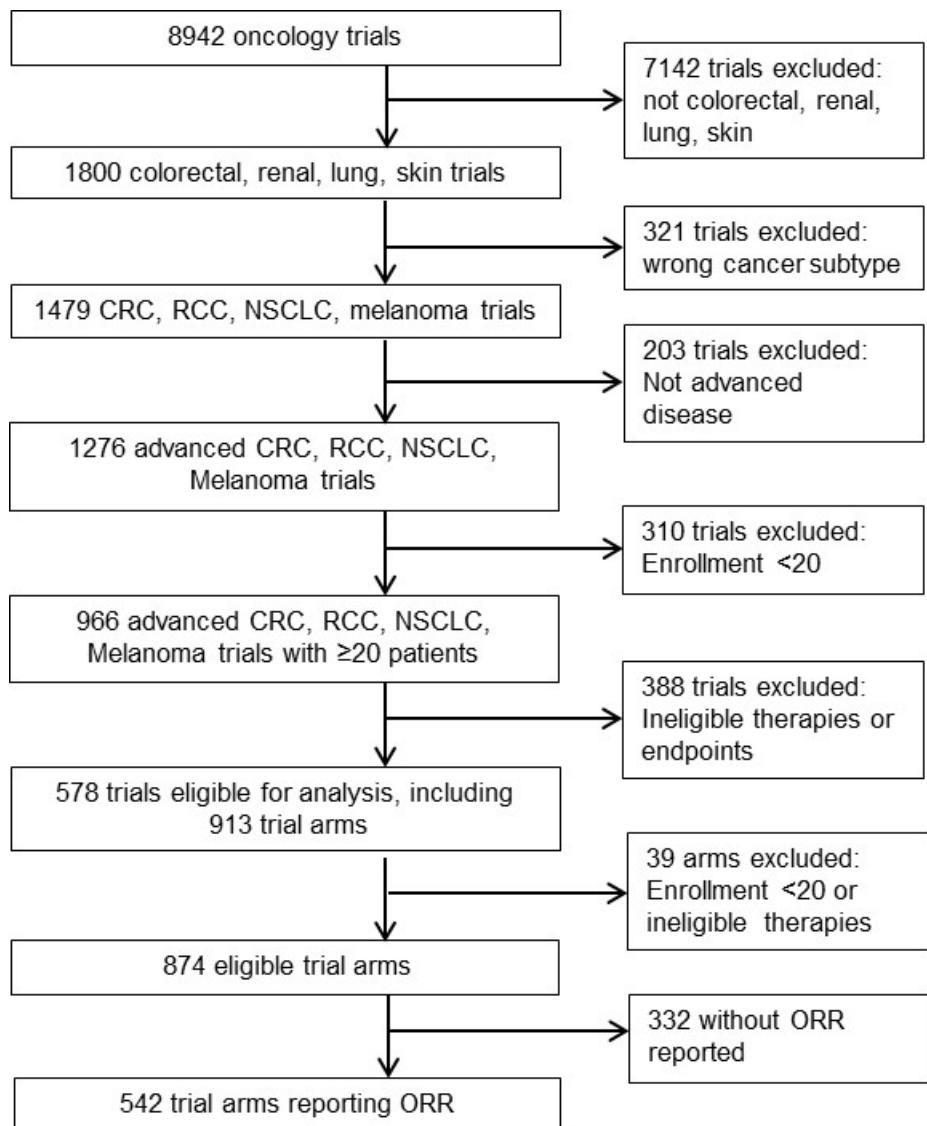
**eTable 1.** Characteristics of trial arms studied

	<b>Eligible arms with ORR</b>	<b>Eligible arms without ORR</b>	<b>p</b>
<b>Arms</b>	542	332	
Cancer type			P<0.001
NSCLC	249 (46%)	194 (59%)	
CRC	151 (28%)	57 (17%)	
Melanoma	71 (13%)	60 (18%)	
RCC	71 (13%)	21 (6%)	
Phase			P= 0.002
Phase 1	36 (7%)	30 (9%)	
Phase 1/2	44 (8%)	36 (11%)	
Phase 2	325 (60%)	206 (62%)	
Phase 2/3	1 (0%)	6 (2%)	
Phase 3	118 (22%)	43 (13%)	
Phase 4	10 (2%)	3 (1%)	
Other	8 (1%)	8 (2%)	
Line of therapy			
First line	251 (46%)	144 (44%)	P=0.533
Second line	237 (44%)	158 (48%)	
Other / any line	54 (10%)	30 (9%)	
<b>Regimens</b>	294	425	
Regimen type			
Single Agent	81 (28%)	28 (21%)	P=0.220
Combination	213 (72%)	103 (79%)	
Regulatory approval?			
Yes	43 (15%)	2 (2%)	P<0.001
No	251 (85%)	129 (98%)	
<b>Enrollment</b>			
Median	52		
Range	20-5394		
Inter-quartile range	36-98		

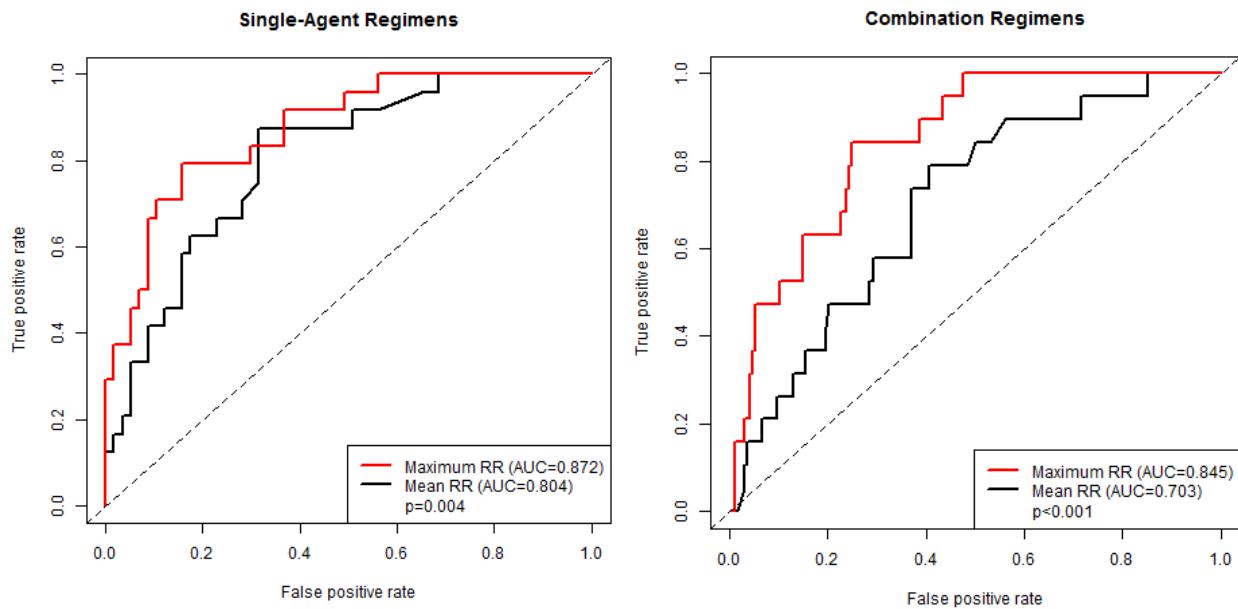
**eTable 2.** Single agents with the highest max objective response rate (ORR) statistically exceeded.

Regimen	Reported ORR	Max ORR exceeded	Regulatory approval and endpoint	Companion diagnostic
Erlotinib in NSCLC	83% n=82	73%	FDA approval based on OS improvement	No (added later)
Crizotinib in NSCLC	74% n=172	67%	Accelerated FDA approval based on ORR, full approval based on PFS improvement	Yes
Gefitinib in NSCLC	70% n=106	60%	EMA approval based on PFS (also approved by FDA since data lock)	Yes
Afatinib in NSCLC	56% n=230	49%	FDA approval based on PFS improvement	Yes
Dabrafenib in melanoma	59% n=79	47%	FDA approval based on PFS improvement	Yes
Axitinib in RCC	56% n=91	45%	FDA approval based on PFS improvement	No
Vemurafenib in melanoma	52% n=132	43%	FDA approval based on OS improvement	Yes
Dacomitinib in NSCLC	54% n=89	43%	No regulatory approval	N/A
Sunitinib in RCC	53% n=36	35%	Accelerated FDA approval based on ORR, full approval based on PFS improvement	No

OS: Overall survival; PFS: Progression free survival; FDA: US Food and Drug Administration;  
 EMA: European Medicines Agency



**eFigure 1.** 1800 trials studying colorectal, renal, lung, and skin malignancies were identified from a database of 8942 oncology trials. From 578 trials eligible for analysis, 874 eligible treatment arms were studied, 542 of which reported response rate per RECIST.



**eFigure 2.** Receiver operating characteristic (ROC) curves describing the characteristics of maximum (red) and mean (black) objective response rate (RR) as diagnostic tests for the prediction of regulatory approval. For both single agent therapies (A) and combination therapies (B), maximum RR has a significantly higher area under the curve (AUC) when compared with a U test.<sup>20</sup>

**eMethods.** R code of the statistical analyses

```
library(plotrix)
library(sm)
library(clinfun)

#we are unable to provide the data set but
#its structure is shown below

#names(d1)
#[1] "ID"                      "NCT_ID"                  "Cancer_code"
#"Arm.enrollment"
#[5] "Regimen_ID"               "Regimen_code"             "Single.agent."
#"Response.rate"
#[9] "Approved."                "X1st.2nd.in.class"

#t1 is a 2x2 table: rows marker cols ref std
accuracy=function(t1){
  tp=t1[2,2];tn=t1[1,1];fp=t1[2,1];fn=t1[1,2]
  tot=tp+tn+fp+fn
  sens=binom.test(tp,tp+fn)
  spec=binom.test(tn,tn+fp)
  ppv=binom.test(tp,tp+fp)
  npv=binom.test(tn,tn+fn)
  ret.mat=matrix(NA,nrow=4,ncol=3)
  ret.mat[1,1]=sens$estimate
  ret.mat[1,2:3]=sens$conf.int[1:2]
  ret.mat[2,1]=spec$estimate
  ret.mat[2,2:3]=spec$conf.int[1:2]
  ret.mat[3,1]=ppv$estimate
  ret.mat[3,2:3]=ppv$conf.int[1:2]
  ret.mat[4,1]=npv$estimate
  ret.mat[4,2:3]=npv$conf.int[1:2]
  rownames(ret.mat)=c("Sensitivity","Specificity","PPV","NPV")
  colnames(ret.mat)=c("Estimate","Lower 95%","Upper 95%")
  invisible(ret.mat)
  print(ret.mat,digits=3)
}

d1$rr=100*d1$Response.rate
##conf bounds
temp=matrix(NA,nrow=nrow(d1),ncol=2)
for(i in 1:nrow(d1))

  temp[i,]=binom.test(round(d1$Response.rate[i]*d1$Arm.enrollment[i]),d1$Arm.enrollment[i])$conf.int

  d1$lower=100*temp[,1]
  d1$upper=100*temp[,2]

##regimen based
```

```

rrmean=with(d1,tapply(rr,Regimen_ID,mean))
rrmedian=with(d1,tapply(rr,Regimen_ID,median))
rrmin=with(d1,tapply(rr,Regimen_ID,min))
rrmax=with(d1,tapply(rr,Regimen_ID,max))
rrmxlb=with(d1,tapply(lower,Regimen_ID,max))
rrwtmn=sapply(split(d1,d1$Regimen_ID),
              function(x) weighted.mean(x$rr,x$Arm.enrollment))

wtmnci = function(x,w){
  wmn = sum(w*x)/sum(w)
  wsd = sum(w*(x-wmn)^2)/sum(w)
  ciло = wmn - 1.96*wsd/sum(w)
}

rrwtmnclo = sapply(split(d1,d1$Regimen_ID),
                    function(x) wtmnci(x$rr,x$Arm.enrollment))

d2=merge(d1,cbind(rrmax,rrwtmn,rrmxlb,rrwtmnclo),by.x=5,by.y=0)
d3=d2[order(d2$Arm.enrollment),]

tapply(d1$Response.rate,d1$Approved.,summary)
boxplot(d1$Response.rate~d1$Approved.)
table(d1$Approved.)

#based on RR
sink("single.agent.txt")
print("Columns are Approved (1) vs Not (0)")
print("Rows are Response Rate<=Cutoff vs >Cutoff")
for(i in seq(10,80,10)){
  print("-----")
  print(paste("Cutoff =",i))
  t1=table(d1$rr[d1$Single.agent.==1]>i,d1$Approved[d1$Single.agent.==1])
  print(t1)
  accuracy(t1)
}
sink()

sink("combination.txt")
print("Columns are Approved (1) vs Not (0)")
print("Rows are Response Rate<=Cutoff vs >Cutoff")
for(i in seq(10,80,10)){
  print("-----")
  print(paste("Cutoff =",i))
  t1=table(d1$rr[d1$Single.agent.==0]>i,d1$Approved[d1$Single.agent.==0])
  print(t1)
  accuracy(t1)
}
sink()

#based on max lower bound
w1=which(!duplicated(d2$Regimen_ID))
d5=d2[w1,]

sink("single.agent.maxlb.txt")
print("Columns are Approved (1) vs Not (0)")
print("Rows are Response Rate<=Cutoff vs >Cutoff")

```

```

for(i in seq(10,70,5)){
  print("-----")
  print(paste("Cutoff =",i))
  t1=table(d5$rrmxlb[d5$Single.agent.==1]>i,d5$Approved[d5$Single.agent.==1])
  print(t1)
  accuracy(t1)
}
sink()

sink("combination.maxlb.txt")
print("Columns are Approved (1) vs Not (0)")
print("Rows are Response Rate<=Cutoff vs >Cutoff")
for(i in seq(10,70,5)){
  print("-----")
  print(paste("Cutoff =",i))
  t1=table(d5$rrmxlb[d5$Single.agent.==0]>i,d5$Approved[d5$Single.agent.==0])
  print(t1)
  accuracy(t1)
}
sink()

r1=roc.curve(d4$rrwtmn[d4$Single.agent.==0],d4$Approved[d4$Single.agent.==0])
r2=roc.curve(d4$rrmxlb[d4$Single.agent.==0],d4$Approved[d4$Single.agent.==0])
r3=roc.curve(d4$rrwtmnclo[d4$Single.agent.==0],
             d4$Approved[d4$Single.agent.==0])
roc.area.test(cbind(d4$rrwtmn[d4$Single.agent.==1],
                     d4$rrmxlb[d4$Single.agent.==1]),
              d4$Approved[d4$Single.agent.==1])

#pdf("2015 single agent roc curve.pdf")
tiff("2015 single agent roc curve.tiff")
plot(r1,lwd=2,col=1,main="Single-Agent Regimens")
lines(r2,lwd=2,col=2)
abline(0,1,lty=2)
legend("bottomright",c("Maximum RR (AUC=0.872)", "Mean RR
(AUC=0.804)", "p=0.004"),
       col=2:0,lty=1,lwd=2)
dev.off()

r1=roc.curve(d4$rrwtmn[d4$Single.agent.==0],d4$Approved[d4$Single.agent.==0])
r2=roc.curve(d4$rrmxlb[d4$Single.agent.==0],d4$Approved[d4$Single.agent.==0])
roc.area.test(cbind(d4$rrwtmn[d4$Single.agent.==0],
                     d4$rrmxlb[d4$Single.agent.==0]),
              d4$Approved[d4$Single.agent.==0])

#pdf("2015 combination roc curve.pdf")
tiff("2015 combination roc curve.tiff")
plot(r1,lwd=2,col=1,main="Combination Regimens")
lines(r2,lwd=2,col=2)
abline(0,1,lty=2)
legend("bottomright",c("Maximum RR (AUC=0.845)", "Mean RR
(AUC=0.703)", "p<0.001"),
       col=2:0,lty=1,lwd=2)

```

```

dev.off()

## per regimen plots

temp=d2[order(d2$Regimen_ID),]
d4=temp[cumsum(rle(temp$Regimen_ID)$lengths),]
write.csv(d2,"2015.regimen.rr.csv")

d4$Number.of.Arms = rle(temp$Regimen_ID)$lengths
d4. = d4[, -c(2:5, 8, 10)]
write.csv(d4., "regimens.csv")

names(d2)
table(d2[, 4])

d2colon = d2[d2$Cancer_code == "C", ]
tempcolon=d2colon[order(d2colon$Regimen_ID),]
d4colon=tempcolon[cumsum(rle(tempcolon$Regimen_ID)$lengths),]
with(d4colon[d4colon$Single.agent==0, ], roc.curve(rrmxlb,Approved.))
with(d4colon[d4colon$Single.agent==1, ], roc.curve(rrmxlb,Approved.))

d2lung = d2[d2$Cancer_code == "L", ]
templung=d2lung[order(d2lung$Regimen_ID),]
d4lung=templung[cumsum(rle(templung$Regimen_ID)$lengths),]
with(d4lung[d4lung$Single.agent==0, ], roc.curve(rrmxlb,Approved.))
with(d4lung[d4lung$Single.agent==1, ], roc.curve(rrmxlb,Approved.))

h.select(x=d4$rrmxlb,y=factor(d4$Approved),hstart=5,hend=100,method="cv")
h.select(x=d4$rrmxlb[d4$Single.agent.==0],y=factor(d4$Approved[d4$Single.agent.==0]),
         hstart=5,hend=100,method="cv")
h.select(x=d4$rrmxlb[d4$Single.agent.==1],y=factor(d4$Approved[d4$Single.agent.==1]),
         hstart=5,hend=100,method="cv")

#####
cor.test(d4$rrmxlb,d4$Approved,method="k")
cor.test(d4$rrmxlb[d4$Single.agent.==0],d4$Approved[d4$Single.agent.==0],
         method="k")
cor.test(d4$rrmxlb[d4$Single.agent.==1],d4$Approved[d4$Single.agent.==1],
         method="k")
cor.test(d4$rrwtmn,d4$Approved,method="k")
cor.test(d4$rrwtmn[d4$Single.agent.==0],d4$Approved[d4$Single.agent.==0],
         method="k")
cor.test(d4$rrwtmn[d4$Single.agent.==1],d4$Approved[d4$Single.agent.==1],
         method="k")

#pdf("2015 All Studies MaxLB.pdf")
tiff("2015 All Studies MaxLB.tiff")
plot(d4$rrmxlb,d4$Approved,type="n",main="All Regimens",
      xlab="Response Rate",ylab="Probability of Approval",xlim=c(0,80))
sm.binomial(d4$rrmxlb,d4$Approved,h=35,xlim=c(0,100),display="se",lwd=2,add=T)

```

```

text(5,0.85,expression(paste(tau,"=0.27")))
text(5,0.75,"p<0.001")
dev.off()

#pdf("2015 Combination Studies MaxLB.pdf")
tiff("2015 Combination Studies MaxLB.tiff")
plot(d4$rrmxlb[d4$Single.agent.==0],d4$Approved[d4$Single.agent.==0],
      xlim=c(0,80),type="n",xlab="Response Rate",
      main="Combination Regimens",ylab="Probability of Approval")
sm.binomial(d4$rrmxlb[d4$Single.agent.==0],d4$Approved[d4$Single.agent.==0],
            lwd=2,h=35,add=T,display="se")
text(5,0.85,expression(paste(tau,"=0.28")))
text(5,0.75,"p<0.001")
dev.off()

#pdf("2015 Single Agent MaxLB.pdf")
tiff("2015 Single Agent MaxLB.tiff")
plot(d4$rrmxlb[d4$Single.agent.==1],d4$Approved[d4$Single.agent.==1],
      xlim=c(0,80),xlab="Response Rate",main="Single-Agent Regimens",
      ylab="Probability of Approval",type="n")
sm.binomial(d4$rrmxlb[d4$Single.agent.==1],d4$Approved[d4$Single.agent.==1],
            h=28,lwd=2,display="se",add=T)
text(5,0.85,expression(paste(tau,"=0.49")))
text(5,0.75,"p<0.001")
dev.off()

#pdf("2015 All Studies WtMean.pdf")
tiff("2015 All Studies WtMean.tiff")
plot(d4$rrwtn,d4$Approved,type="n",main="All Regimens",
      xlab="Response Rate",ylab="Probability of Approval",xlim=c(0,80))
sm.binomial(d4$rrwtn,d4$Approved,h=35,display="se",lwd=2,add=T)
text(5,0.85,expression(paste(tau,"=0.12")))
text(5,0.75,"p=0.012")
dev.off()

#pdf("2015 Combination Studies WtMean.pdf")
tiff("2015 Combination Studies WtMean.tiff")
plot(d4$rrwtn[d4$Single.agent.==0],d4$Approved[d4$Single.agent.==0],
      xlim=c(0,80),type="n",xlab="Response Rate",
      main="Combination Regimens",ylab="Probability of Approval")
sm.binomial(d4$rrwtn[d4$Single.agent.==0],d4$Approved[d4$Single.agent.==0],
            lwd=2,display="se",h=35,add=T)
text(5,0.85,expression(paste(tau,"=0.17")))
text(5,0.75,"p=0.003")
dev.off()

#pdf("2015 Single Agent WtMean.pdf")
tiff("2015 Single Agent WtMean.tiff")
plot(d4$rrwtn[d4$Single.agent.==1],d4$Approved[d4$Single.agent.==1],
      xlim=c(0,80),xlab="Response Rate",main="Single-Agent Regimens",
      ylab="Probability of Approval",type="n")
sm.binomial(d4$rrwtn[d4$Single.agent.==1],d4$Approved[d4$Single.agent.==1],
            h=28,lwd=2,display="se",add=T)
text(5,0.85,expression(paste(tau,"=0.41")))
text(5,0.75,"p<0.001")
dev.off()

```

```

h.select(x=d4$rrwtnmclo,y=factor(d4$Approved),hstart=5,hend=100,method="cv")
h.select(x=d4$rrwtnmclo[d4$Single.agent.==0],y=factor(d4$Approved[d4$Single.agent.==0]),
         hstart=5,hend=100,method="cv")
h.select(x=d4$rrwtnmclo[d4$Single.agent.==1],y=factor(d4$Approved[d4$Single.agent.==1]),
         hstart=5,hend=100,method="cv")

cor.test(d4$rrwtnmclo,d4$Approved,method="k")
cor.test(d4$rrwtnmclo[d4$Single.agent.==0],d4$Approved[d4$Single.agent.==0],
         method="k")
cor.test(d4$rrwtnmclo[d4$Single.agent.==1],d4$Approved[d4$Single.agent.==1],
         method="k")

tiff("2015 All Studies WtMeanLB.tiff")
plot(d4$rrwtnmclo,d4$Approved,type="n",main="All Regimens",
      xlab="Response Rate",ylab="Probability of Approval",xlim=c(0,80))
sm.binomial(d4$rrwtnmclo,d4$Approved,h=25,display="se",lwd=2,add=T)
text(5,0.85,expression(paste(tau,"=0.12")))
text(5,0.75,"p=0.012")
dev.off()

tiff("2015 Combination Studies WtMeanLB.tiff")
plot(d4$rrwtnmclo[d4$Single.agent.==0],d4$Approved[d4$Single.agent.==0],
      xlim=c(0,80),type="n",xlab="Response Rate",
      main="Combination Regimens",ylab="Probability of Approval")
sm.binomial(d4$rrwtnmclo[d4$Single.agent.==0],d4$Approved[d4$Single.agent.==0],
      lwd=2,display="se",h=35,add=T)
text(5,0.85,expression(paste(tau,"=0.17")))
text(5,0.75,"p=0.003")
dev.off()

tiff("2015 Single Agent WtMeanLB.tiff")
plot(d4$rrwtnmclo[d4$Single.agent.==1],d4$Approved[d4$Single.agent.==1],
      xlim=c(0,80),xlab="Response Rate",main="Single-Agent Regimens",
      ylab="Probability of Approval",type="n")
sm.binomial(d4$rrwtnmclo[d4$Single.agent.==1],d4$Approved[d4$Single.agent.==1],
      h=28,lwd=2,display="se",add=T)
text(5,0.85,expression(paste(tau,"=0.40")))
text(5,0.75,"p<0.001")
dev.off()

cor(d4$rrwtnmclo,d4$rrmxlb)

h.select(x=d4lung$rrwtnm,y=factor(d4lung$Approved),
         hstart=5,hend=100,method="cv")
h.select(x=d4lung$rrwtnm[d4lung$Single.agent.==0],
         y=factor(d4lung$Approved[d4lung$Single.agent.==0]),hstart=5,hend=100,
         method="cv")
h.select(x=d4lung$rrwtnm[d4lung$Single.agent.==1],
         y=factor(d4lung$Approved[d4lung$Single.agent.==1]),
         hstart=5,hend=100,method="cv")

```

```

cor.test(d4lung$rrwtnn,d4lung$Approved,method="k")
cor.test(d4lung$rrwtnn[d4lung$Single.agent.==0],
         d4lung$Approved[d4lung$Single.agent.==0],method="k")
cor.test(d4lung$rrwtnn[d4lung$Single.agent.==1],
         d4lung$Approved[d4lung$Single.agent.==1],method="k")

tiff("2015 Lung All WtMean.tiff")
plot(d4lung$rrwtnn,d4lung$Approved,type="n",main="All Regimens",
      xlab="Response Rate",ylab="Probability of Approval",xlim=c(0,80))
sm.binomial(d4lung$rrwtnn,d4lung$Approved,h=30,display="se",lwd=2,add=T)
text(5,0.85,expression(paste(tau,"=0.04")))
text(5,0.75,"p=0.598")
dev.off()

tiff("2015 Lung Combination WtMean.tiff")
plot(d4lung$rrwtnn[d4lung$Single.agent.==0],
      d4lung$Approved[d4lung$Single.agent.==0],xlim=c(0,80),type="n",
      xlab="Response Rate",main="Combination Regimens",
      ylab="Probability of Approval")
sm.binomial(d4lung$rrwtnn[d4$Single.agent.==0],
            d4lung$Approved[d4$Single.agent.==0],lwd=2,display="se",
            h=20,add=T)
text(5,0.85,expression(paste(tau,"=0.06")))
text(5,0.75,"p=0.454")
dev.off()

tiff("2015 Lung Single Agent WtMean.tiff")
plot(d4lung$rrwtnn[d4lung$Single.agent.==1],
      d4lung$Approved[d4lung$Single.agent.==1],xlim=c(0,80),type="n",
      xlab="Response Rate",main="Combination Regimens",
      ylab="Probability of Approval")
sm.binomial(d4lung$rrwtnn[d4$Single.agent.==1],
            d4lung$Approved[d4$Single.agent.==1],lwd=2,display="se",
            h=20,add=T)
text(5,0.85,expression(paste(tau,"=0.55")))
text(5,0.75,"p=0.002")
dev.off()

h.select(x=d4colon$rrwtnn,y=factor(d4colon$Approved),
          hstart=5,hend=100,method="cv")
h.select(x=d4colon$rrwtnn[d4colon$Single.agent.==0],
          y=factor(d4colon$Approved[d4colon$Single.agent.==0]),hstart=5,hend=100,
          method="cv")
h.select(x=d4colon$rrwtnn[d4colon$Single.agent.==1],
          y=factor(d4colon$Approved[d4colon$Single.agent.==1]),hstart=5,hend=100,method="cv")

cor.test(d4colon$rrwtnn,d4colon$Approved,method="k")
cor.test(d4colon$rrwtnn[d4colon$Single.agent.==0],
         d4colon$Approved[d4colon$Single.agent.==0],method="k")
cor.test(d4colon$rrwtnn[d4colon$Single.agent.==1],
         d4colon$Approved[d4colon$Single.agent.==1],method="k")

tiff("2015 colon All WtMean.tiff")
plot(d4colon$rrwtnn,d4colon$Approved,type="n",main="All Regimens",

```

```

    xlab="Response Rate",ylab="Probability of Approval",xlim=c(0,80))
sm.binomial(d4colon$rrwtnn,d4colon$Approved,h=45,display="se",lwd=2,add=T)
text(5,0.85,expression(paste(tau,"=0.17")))
text(5,0.75,"p=0.005")
dev.off()

tiff("2015 colon Combination WtMean.tiff")
plot(d4colon$rrwtnn[d4colon$Single.agent.==0],
      d4colon$Approved[d4colon$Single.agent.==0],xlim=c(0,80),type="n",
      xlab="Response Rate",main="Combination Regimens",
      ylab="Probability of Approval")
sm.binomial(d4colon$rrwtnn[d4$Single.agent.==0],
            d4colon$Approved[d4$Single.agent.==0],lwd=2,display="se",
            h=45,add=T)
text(5,0.85,expression(paste(tau,"=0.23")))
text(5,0.75,"p=0.015")
dev.off()

tiff("2015 colon Single Agent WtMean.tiff")
plot(d4colon$rrwtnn[d4colon$Single.agent.==1],
      d4colon$Approved[d4colon$Single.agent.==1],xlim=c(0,80),type="n",
      xlab="Response Rate",main="Combination Regimens",
      ylab="Probability of Approval")
sm.binomial(d4colon$rrwtnn[d4$Single.agent.==1],
            d4colon$Approved[d4$Single.agent.==1],lwd=2,display="se",
            h=20,add=T)
text(5,0.85,expression(paste(tau,"=0.55")))
text(5,0.75,"p=0.002")
dev.off()

h.select(x=d4colon$rrmax,y=factor(d4colon$Approved),
          hstart=5,hend=100,method="cv")
cor.test(d4colon$rrmax,d4colon$Approved,method="k")

tiff("2015 colon All MaxORR.tiff")
plot(d4colon$rrmax,d4colon$Approved,type="n",main="All Regimens",
      xlab="Response Rate",ylab="Probability of Approval",xlim=c(0,80))
sm.binomial(d4colon$rrmax,d4colon$Approved,h=15,display="se",lwd=2,add=T)
text(5,0.85,expression(paste(tau,"=0.25")))
text(5,0.75,"p=0.004")
dev.off()

h.select(x=d4lung$rrmax,y=factor(d4lung$Approved),
          hstart=5,hend=100,method="cv")
cor.test(d4lung$rrmax,d4lung$Approved,method="k")

tiff("2015 lung All MaxORR.tiff")
plot(d4lung$rrmax,d4lung$Approved,type="n",main="All Regimens",
      xlab="Response Rate",ylab="Probability of Approval",xlim=c(0,80))
sm.binomial(d4lung$rrmax,d4lung$Approved,h=20,display="se",lwd=2,add=T)
text(5,0.85,expression(paste(tau,"=0.23")))
text(5,0.75,"p=0.003")
dev.off()

library(rmeta)

```

```

w1=which(d1$Regimen_code=="L-Erlotinib")
f1=d1[w1,]
f2=f1[order(f1$Arm.enrollment),]
f2$se=sqrt((f2$Response.rate)*(1-f2$Response.rate)/f2$Arm.enrollment)
f2$Arm.enroll=f2$Arm.enrollment
f2$Arm.enroll[f2$Arm.enrollment>5000]=434
d4[which(d4$Regimen_code=="L-Erlotinib"),]
#pdf("forest erlotinib.pdf")
#jpeg("forest erlotinib.jpg",width=720,height=720,res=100)
tiff("forest erlotinib.tiff")
metaplot(f2$Response.rate,f2$se,nn=f2$Arm.enroll,
         xlab="Response Rate",ylab="",xlim=c(0,1),main="Erlotinib")
;text(0.2,-24,"*",cex=2)
segments(.13,-30,.13,-25,col=2,lwd=5)
segments(.73,-30,.73,-25,col=4,lwd=5)
;text(0.05,-25,"13%",cex=1.5,col=2)
;text(0.8,-25,"73%",cex=1.5,col=4)
dev.off()

w1=which(d1$Regimen_code=="L-Docetaxel")
f1=d1[w1,]
f2=f1[order(f1$Arm.enrollment),]
f2$se=sqrt((f2$Response.rate)*(1-f2$Response.rate)/f2$Arm.enrollment)
f2[2,14]=0.041
d4[which(d4$Regimen_code=="L-Docetaxel"),]
#pdf("forest docetaxel.pdf")
#jpeg("forest docetaxel.jpg",width=720,height=720,res=100)
tiff("docetaxel.tiff")
metaplot(f2$Response.rate,f2$se,nn=f2$Arm.enrollment,
         xlab="Response Rate",ylab="",xlim=c(0,1),main="Docetaxel")
segments(.10,-11,.10,-9,col=2,lwd=5)
segments(.25,-11,.25,-9,col=4,lwd=5)
;text(0.05,-9.5,"10%",cex=1.5,col=2)
;text(0.32,-9.5,"25%",cex=1.5,col=4)
dev.off()

w1=which(d1$Regimen_code=="L-Carboplatin; Paclitaxel")
f1=d1[w1,]
f2=f1[order(f1$Arm.enrollment),]
f2$se=sqrt((f2$Response.rate)*(1-f2$Response.rate)/f2$Arm.enrollment)
f2[3,14]=0.040
d4[which(d4$Regimen_code=="L-Carboplatin; Paclitaxel"),]
#pdf("forest carboplatin paclitaxel.pdf")
#jpeg("forest carboplatin paclitaxel.jpg",width=720,height=720,res=100)
tiff("forest carboplatin paclitaxel.tiff")
metaplot(f2$Response.rate,f2$se,nn=f2$Arm.enrollment,
         xlab="Response Rate",ylab="",xlim=c(0,1),main="Carboplatin
Paclitaxel")
segments(.28,-20,.28,-15,col=2,lwd=5)
segments(.31,-20,.31,-15,col=4,lwd=5)
;text(0.22,-16,"28%",cex=1.5,col=2)
;text(0.37,-16,"31%",cex=1.5,col=4)
dev.off()

w1=which(d1$Regimen_code=="L-Pemetrexed")
f1=d1[w1,]
f2=f1[order(f1$Arm.enrollment),]

```

```
f2$se=sqrt((f2$Response.rate)*(1-f2$Response.rate)/f2$Arm.enrollment)
f2[3,14]=0.040
pdf("forest pemetrexed.pdf")
jpeg("forest carboplatin paclitaxel.jpg",width=720,height=720,res=100)
metaplot(f2$Response.rate,f2$se,nn=f2$Arm.enrollment,
         xlab="Response Rate",ylab="",xlim=c(0,1),main="Pemetrexed")
dev.off()

#single agent exceeding 30-40 percent
```